Clinical heterogeneity in familial Alzheimer's disease

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Two studies of non-amnestic manifestations of autosomal dominant familial Alzheimer's disease (ADAD) are reported in *The Lancet Neurology*.[1,2] In the first study, Mengxuan Tang and colleagues[1] report, on behalf of the Dominantly Inherited Alzheimer Network (DIAN) consortium, a combined description of the DIAN observational study (DIAN-OBS) cohort and the scientific literature.[1] In the second study, Natalie Ryan and colleagues[2] describe heterogeneous cognitive symptoms and neurological features in a large series of participants that were referred to the Dementia Research Centre in London, UK, over many years.

Tang and colleagues[1] compare individual data from 1228 patients with ADAD (753 with detailed clinical data) with data from the DIAN-OBS cohort. They found that non-cognitive features, such as myoclonus and seizures, were commonly observed in patients reported on in the published work (each in approximately one of five patients). By contrast, motor features were far less common in the 107 symptomatic patients in the DIAN-OBS cohort (9% had myoclonus and 3% had seizures). Findings were inverted for non-amnestic cognitive symptoms: atypical presentations of aphasia, visual agnosia, and behavioural changes were quite common in the DIAN-OBS cohort (>50%) but were far more rare in the patients described in the published work (<30%).

Ryan and colleagues[2] describe a large case series of 213 patients with *PSEN1* or *APP* mutations (detailed medical history was available for 121 only). Myoclonus and seizures were the most common non-cognitive neurological features, with myoclonus—observed in 33% of individuals with *APP* mutations and 47% of individuals with *PSEN1* mutations—being a significant risk factor for seizures (occurring in about one in four patients). Individuals with *APP* mutations almost invariably had amnestic presentations (97%); by contrast, amnestic symptoms were significantly less common in patients with *PSEN1* mutations (84%; p=0·037). Of note, even though Ryan and colleagues describe the non-amnestic presentations in patients with *PSEN1* mutations as common, these non-amnestic presentations were far less common in their case series (16% in *PSEN1*, 3% in *APP*) than in DIAN-OBS (>50%). As such, Ryan and colleagues' case series is similar to as described in the analysis of the literature by Tang and colleagues. It is not evident what explains these differences, but methodological aspects, particularly selection bias and measurement bias,[3] probably contribute to the difference in observed prevalence, as noted by both groups of authors.

Both Articles share the important message that recognising clinical heterogeneity in Alzheimer's disease is crucial. An accurate diagnosis is of great importance because this is the starting point for best patient management. Heterogeneity in Alzheimer's disease needs to be recognised because diagnoses are too often missed in patients with atypical presentations, and understanding heterogeneity might provide keys to finding treatments. Also, a substantial proportion of patients with sporadic Alzheimer's disease have non-amnestic presentations, such as visual agnosia, aphasia, or dysexecutive or behavioural phenotypes.[4–6] Clinicians should be aware that memory can be relatively spared in Alzheimer's disease until advanced stages of the disease. Particularly in patients with an atypical presentation or an atypical age at onset, diagnosis is often missed because many professionals do not think of Alzheimer's disease when they see a 50 year old complaining of losing track of deadlines at work or having difficulty mastering a novel software package. The likelihood of an atypical presentation gradually increases with a younger age at onset.[7] Patients with an onset later than 80 years typically present with early and prominent amnestic problems, but in those with an onset before the age of 65 years, atypical presentations occur in roughly one of three patients.[8,9]

The latest diagnostic criteria reflect these findings; the National Institute on Aging—Alzheimer's Association (NIA-AA) criteria and the International Working Group (IWG) criteria no longer require memory impairment for a clinical diagnosis of Alzheimer's disease, as they recognise that Alzheimer's disease might also start with deficits in other cognitive domains.[10,11] Additionally, the NIA-AA criteria list changes in personality, behaviour, or comportment as a fifth cognitive domain. These criteria fit the observations in the study by Tang and colleagues, who observed changes in personality and behaviour in 61% of the DIAN participants and 32% of the cases described in the published work. However, a

drawback of listing these changes as a fifth cognitive domain is that it is quite difficult to establish norms or cut offs. When is behaviour so abnormal that it should count as an impaired domain on which to establish a diagnosis of dementia? In the course of dementia, almost every patient encounters behavioural problems to some extent, which might be intrinsically caused by the disease process or be a reaction their experience of ongoing decline. By contrast to changes in cognition, behavioural impairment does not show a monotonic decline with the disease process, but rather has a sinoid-like course. For example, a patient might experience depression early on, but, as the disease progresses, their mood may actually lift. Additionally, behavioural symptoms come and go over the course of disease, and symptoms such as delusions or aberrant motor activity might develop at any time. Neither the NIA-AA or IWG criteria mentions non-cognitive neurological features in the diagnosis of Alzheimer's disease, other than in the context of mixed dementia due to stroke or Lewy body pathology. These neurological features seem to only present in a later stage of the disease and hence are of less relevance for diagnosis.

Heterogeneity in manifestation might reflect variation in underlying molecular pathways, and disentangling the various routes to dementia due to Alzheimer's disease could ultimately lead to different therapeutic strategies tailored to specific patient groups. As a first possibility, the heterogeneity in clinical presentation might be due to mixed pathology. For example, in late-onset Alzheimer's disease mixed disease is the norm rather than the exception, and co-occurring Lewy body pathology or vascular pathology might contribute to clinical heterogeneity. If patients present with mixed disease, it would seem logical to target treatment for each of the contributing pathologies, rather than base treatment strategies on the prevailing clinical diagnosis alone.[12] However, mixed disease cannot be the only explanation for clinical heterogeneity. This is illustrated by the fact that clinical heterogeneity is even more common in patients with an early age of onset, and within the spectrum of Alzheimer's disease, vulnerability of brain regions to disease seems to vary among patients. For example, although most patients with Alzheimer's disease have a predominantly temporal distribution of pathology, pathology is more posterior in others.

These studies[1,2] support this idea that even monogenetic forms of the disease do not present with one uniform manifestation. Although Tang and colleagues report that mutation type was related in some extent to variation in age at onset and Ryan and colleagues report an association with likelihood of atypical cognitive symptoms, this did not explain a large proportion of the observed heterogeneity. Instead, the origin of the observed variability in pathology could lie in other factors (eg, environmental, metabolic, or epigenetic). A second possibility is that the heterogeneity observed in these two studies does have a genetic origin, with genes other than the major causative ones contributing to variations in vulnerability of specific brain regions. As an example, former studies have suggested that *APOE* ε4-negative patients are more likely to present with atypical cognitive symptoms.[7] Developmental factors might also contribute to regional vulnerability. For example, individuals that had language learning disability as a child might be more prone to have a logopenic progressive aphasia related to Alzheimer's disease at a later age.[13] This notion would fit with the general idea that the strength of specific neural networks not only lie at the heart of variability in regional vulnerability,[14-16] but also that strengthening specific neural networks might be at the core of resilience to pathology, and, as such, provide a target for treatment.

The notion that we will find one treatment that cures all patients with Alzheimer's disease is quickly losing ground. Far more likely is the idea that in the future, specific subtypes of Alzheimer's disease could benefit from specific medications. To attain that goal, recognition and deep understanding of heterogeneity in clinical manifestation of Alzheimer's disease is a necessary step.

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Searching for the mechanisms of consciousness in epilepsy

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Defining and understanding consciousness is often assumed to be similar to searching for the Holy Grail. The term consciousness has many ambiguous meanings and often, in medicine, awareness or responsiveness (or lack thereof) are used as surrogate markers. Epileptic seizures provide an opportunity to study these types of changes as part of the consciousness experience. In the *Lancet Neurology*, Jennifer Guo and colleagues[1] report the results of their study aimed at discovering the potential neuronal underpinnings of impaired consciousness, as depicted by alterations in awareness or responsivity, in presumed typical absence epilepsy using functional MRI (fMRI) and electroencephalography (EEG), and behavioral testing in children and adolescents aged 5–19 years. The investigators propose that the impairments identified are the result of widespread involvement of the brain, implicating suspension of the default mode network in conjunction with reduced sensory perception, and not because of focal changes. They also suggest that the behavioural impairments might happen at the onset of the seizures.

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To collect an adequate number of patients, the investigators expanded the criteria for absence seizures and probably included patients with different syndromes, as discussed by Panayiotopoulos.[2] The International League Against Epilepsy is proposing a classification of seizures and epilepsies[3,4] and Guo and colleagues provide new insights that might help classification. Their findings suggest a different way of interpreting how changes in impairment of consciousness occur in absence seizures. It is often assumed that the impairment of consciousness occurs if the seizures last more than 3 s, based on the reaction times tested with EEG monitoring.[5] This cutoff was included in the study of the effectiveness of antiseizure medications to define an electroclinical seizure as lasting more than 3 s;[6] the medications were considered